REMARKS

The Applicants would like to thank the Examiner for the withdrawal of the objection to the specification, the rejection to Claim 22 under 35 U.S.C. § 112, second paragraph and the rejection to Claim 23 under 35 U.S.C. § 101.

I. Objection to the Abstract of the disclosure

As requested by the Examiner, the amended abstract has been amended to be a single paragraph and to conform to the standards set forth in MPEP § 608.01(b). The amended abstract is now on a separate sheet of paper.

II. Rejection under 35 U.S.C. § 102(e) under Van Ness *et al.*

The Examiner has rejected Claims 1, 6-9 and 28 under 35 U.S.C. § 102(e) as being anticipated by Van Ness *et al.* (U.S. Patent No. 6,027,890; Issued February 22, 2000, Filed July 22, 1997). Specifically the Examiner asserts that Van Ness *et al.* disclose a method for detecting biomolecules using an array comprising putting into contact a target compound with a capture molecule which are fixed upon a surface of a solid support according to an array with a density of 10^7 to 10^9 biomolecules per 2000 square microns (columns 73 and 76). The Examiner asserts that this is within the scope of "at least 20 discrete regions per cm^2" of Claim 1. Further, the Examiner asserts that the performing of a reaction leading to the formation of a precipitate of 50 micrometer spots (column 76) is within the scope of "a few micrometers from the bound target" as is determining the presence of precipitates with a device such as a CCD-linked microscope (column 76, lines 31-44).

The present invention, as recited in amended Claim 1 is a "method for the identification and/or the quantification of a target compound obtained from a sample, , comprising the steps of: putting into contact the target compound with a capture molecule in order to allow a specific binding between said target compound with a capture molecule, said capture molecule being fixed upon a surface of a solid support according to an array comprising a density of at least 20 discrete regions per cm^2, each of said discrete regions being fixed with one species of capture molecules; performing a reaction leading to formation of a precipitate formed at the location of said binding by the deposit of a metallic compound; determining the possible presence of

precipitate(s) in discrete region(s); and correlating the presence of the precipitate(s) at the discrete region(s) with the identification and/or a quantification of said target compound."

Van Ness *et al.* do not disclose a method where the reaction leading to the formation of a precipitate deposits a metallic compound, as required by the present invention in amended Claim 1. Van Ness *et al.* teach methods that make use of a biotin-streptavidin/horseradish peroxide system (column 76), not of the fixation of a metallic compound upon the bound target or by the reduction of a metal in the presence of an enzyme. Therefore, Van Ness *et al.* do not teach all of the elements recited in Claim 1.

In view of the above remarks, the Applicants respectfully request withdrawal of the rejection to Claims 1, 6-9 and 28 under 35 U.S.C. § 102(e).

III. Rejection of Claims 1-26 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-26 under 35 U.S.C. § 103(a) as being unpatentable over Abouzied *et al.* (Journal of AOAC International, Vol. 77, No. 2 (MAR-APR), pp. 495-501, 1994) in view of Howard III *et al.* (EP 0646784A1, May 4, 1995) and Van Ness *et al.*, and further in view of Roth *et al.* (U.S. Patent No. 5,902,727) and Terstappen *et al.* (U.S. Patent No. 5,646,001).

In order for a combination of references to render a claim obvious, the combination of references must provide the motivation to combine these elements to create the claimed invention. *In re Fine*, 5 U.S.P.Q.2d 1597 (Fed. Cir. 1988), *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1456 (Fed. Cir. 1998) and *In re Geiger*, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). As discussed below, the cited combination of references does not provide a motivation to combine the elements to create the claimed invention. Furthermore, the present invention provides significant advantages over the methods disclosed in the cited references.

Initially, Applicants note that the Examiner asserts that the arguments presented in the previous Amendment were not deemed persuasive since the claim limitations were added through amendments. If the cited references do not teach or suggest all of the elements of the claims presented for examination, the claims are not obvious over the cited references. It is immaterial whether the limitations which are not taught in the claims were present in the original claims or whether they were added by amendment. Applicant respectfully submits that the cited references do not teach or suggest all the elements of the claims presented herein.

The cited references do not teach or suggest methods of detecting a precipitate formed by the deposit of a metallic compound at the location of the bound target on an array as recited in amended Claim 1. Applicants note that the support for the amendment to Claim 1 reciting the "precipitate formed at the location of said binding by the deposit of a metallic compound" may be found throughout the specification, including at page 5, line 30 to page 6, line 3, page 8, line 22 to page 10, line 23 and within the Examples. Claim 27 also recites that the formation of the precipitate is at the location of said binding. Applicants note that the use of the terminology "at the location of said binding" is not intended to imply any particular dimensions to the diameter of the precipitate. Rather, this terminology simply means that the dimensions of the precipitate are such that the precipitate may be localized to the location of a single capture molecule on the array (i.e. the dimensions of the precipitate are not so large as to make the identity of the capture molecule at which the precipitate formed ambiguous).

The Abouzied *et al.* reference discloses a colorimetric method of screening and detecting analytes on nitrocellulose (NC) membrane strips. In the method described in Abouzied, a colored reaction product formed through the action of an enzyme linked to the target analyte is used to detect the presence of the analyte in the sample. Abouzied does not teach or suggest methods in which a metallic precipitate is formed. The method of detection includes visually comparing color intensities formed by precipitates on the NC membrane and quantitatively assaying line density using a CCD camera. In addition, in the method disclosed in Abouzied, the lines on the NC membrane strips were spaced 0.25 cm apart (page 496, column 2).

As indicated in the specification at page 2, line 32 through page 3, line 11, colorimetric assays in which an enzyme generates a colored reaction product which forms a precipitate, such as the methods described in Abouzied, are unsuitable for use in arrays comprising a density of at least 20 discrete regions per cm^2 because the precipitate occupies an area which is too large to allow it to be localized to a single discrete region. In contrast, in the present invention, the metallic precipitate forms at the location of the bound target molecule, thereby allowing it to be localized to a single position on an array comprising at least 20 discrete regions per cm^2.

With respect to the apparatus of Claim 14, Applicants note that Abouzied *et al.* discloses a nitrocellulose strip being visualized by a camera which is connected to a computer to detect and/or quantify. However, the nitrocellulose strip of Abouzied, as previously discussed, is not a

solid support comprising an array of at least 20 discrete regions per cm^2 and a precipitate positioned at the location of a bound target compound as recited in amended Claim 14.

Thus, there is no disclosure or suggestion in Abouzied of arrays comprising at least 20 discrete regions per cm^2 nor does this reference disclose or suggest formation of a metallic precipitate at the location of a target compound bound to such arrays or devices comprising such arrays and such precipitates.

Like Abouzied, Roth discloses a method for localizing and quantitating a molecule in a sample. In the method of Roth, an enzyme generates a colored reaction product which precipitates. However, as discussed above, the precipitate generated through enzymatic reactions is too diffuse to be used with an array having a density of at least 20 discrete regions per cm^2 as in the present invention.

Furthermore, although Roth discloses the use of antibodies having gold particles fixed thereto along with silver intensification in the context of localizing a molecule in a cell or tissue, there is no disclosure or suggestion of using such techniques to detect the presence of a precipitate formed at the location of a target compound on an array having a density of at least 20 discrete regions per cm^2 as in the present invention. Furthermore, Roth teaches that methods using gold particles and silver intensification are undesirable or labor intensive in quantitative analyses (see Column 1, line 24-30). Accordingly, Roth teaches away from methods in which a metallic precipitate is used. Thus, there is no disclosure or suggestion in Roth of arrays comprising at least 20 discrete regions per cm^2 nor does this reference disclose or suggest formation of a precipitate at the location of a target compound bound to such arrays or devices comprising such arrays and such precipitates.

Howard III *et al.* disclose a video test strip reader for detecting the presence of molecules bound to a test strip. The device of Howard is not used to detect a precipitate formed on a high density array as in the present invention but rather to read a signal from a test strip. There is no disclosure or suggestion of detecting the presence of a metallic precipitate formed at the location of a target compound on an array having a density of at least 20 discrete regions per cm^2 as in the present invention or devices comprising such arrays and such precipitates.

Furthermore, with respect to the apparatus of Claim 14, although Howard III *et al.* discloses a CCD camera equipped with illumination sources and a computer system (page 5) which can evaluate such information as barcodes, the apparatus disclosed in Howard is used with

a test strip rather than an array having a density of at least 20 discrete regions per cm^2 and having a metallic precipitate formed at the location of a target compound.

Terstappen *et al.* disclose the use of magnetic beads to collect cells. However, there is no disclosure or suggestion in Terstappen of detecting the presence of a metallic precipitate formed at the location of a target compound on an array having a density of at least 20 discrete regions per cm^2 as in the present invention or devices comprising such arrays and such precipitates.

Van Ness *et al.* disclose an array with a density of 10^7 to 10^9 biomolecules per 2000 square microns (columns 73 and 76) and performing of an enzymatic reaction leading to the formation of a precipitate of 50 micrometer spots (column 76). However, there is no disclosure within Van Ness for the detection of a precipitate formed by a metallic compound at the location of the target compound.

Furthermore, as averred in the accompanying Declaration and Exhibits, the methods of the present invention provide significant advantages over the methods disclosed in Van Ness. In particular, the metallic precipitates utilized result in an improvement in sensitivity of over 1000 fold with respect to the methods disclosed in Van Ness (see Exhibit B, demonstrating that the limit of detection of spotted DNA for the metallic precipitate used in the present invention was 0.1 nM, while the peroxidase-based methods of Van Ness had a detection level of 100 nM). In addition, the metallic precipitates utilized in the present invention may be detected in a matter of minutes as opposed to the several hours required to detect the precipitates in the methods of Van Ness (see Exhibit C demonstrating that the metallic precipitate was obtained in 10 minutes as opposed to the peroxidase precipitate, which was formed after 3 hours). The high sensitivity and short reaction time are extremely beneficial in high throughput methods performed on high density arrays.

Furthermore, in the methods disclosed in Van Ness, the spots formed by the non-metallic precipitate resulting from the enzymatic reaction have a diameter of 50 micrometers. Such dimensions are not compatible with the high density arrays utilized in the present methods. In contrast, the metallic precipitates formed in the methods of the present invention may readily be localized to a single position on the high density arrays used in the methods of the present invention.

Because none of the cited references teach or suggest detection of a metallic precipitate formed at the location of a target compound on an array having a density of at least 20 discrete

regions per cm^2 or devices comprising such arrays and such precipitates and because the present invention provides significant advantages over the methods disclosed in the cited references, the cited references do not render the claimed invention obvious.

IV. Rejection of Claims 27-32 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 27-32 under 35 U.S.C. § 103(a) as being unpatentable over Abouzied *et al.*, in view of Van Ness *et al.* and Gingeras *et al.* (U.S. Patent No. 6,228,575). Specifically, the Examiner asserts that it would have been obvious to one of skill in the art such that a CCD camera would have been linked to a computer with a program to recognize such images of discrete regions on the array in order to process the images taken by the camera, and to detect/quantitate the target compounds.

The Abouzied *et al.* reference discloses a method of simultaneously screening and detection of multianalyte using membrane strips (Abstract), wherein a precipitation is formed on the membrane upon binding and detection and quantification of the precipitates by light reflection and video analysis. The image is taken by a CCD video camera and converted into digital form (Abstract and Experimental, pp. 495-497). As discussed above, the methods described in Abouzied are unsuitable for use in arrays comprising a density of at least 20 discrete regions per cm^2 because the non-metallic precipitate utilized in the disclosed methods occupies an area which is too large to allow it to be localized to a single discrete region. Claim 27 requires the formation of a precipitate at a specific location and Claim 28 requires that the precipitate is formed on the surface of a particle associated with the target compound. There is no teaching or suggestion in Abouzied regarding such a specific and discrete presence for the precipitate since Abouzied teaches the formation of a precipitate on a NC membrane strips spaced 0.25 cm apart (page 496, column 2). In contrast, in the present invention, the (metallic) precipitate forms at the location of the bound target molecule, thereby allowing it to be localized to a single position on an array comprising at least 20 discrete regions per cm^2. Furthermore, the precipitate occupies a diameter of about 1 μM.

The Van Ness *et al.* reference discloses the detection of biomolecules using an array and apparatus for the detection which comprises an array on a solid support, a microscope and CCD camera (column 76). As discussed above, Van Ness *et al.* does not disclose the detection of a precipitate formed by a metallic compound at the location of the target compound (Claim 1) or

where the precipitate is formed on the surface of a particle associated with the target compound (Claim 28) or an apparatus which detects the precipitate formed at the location of the target compound (Claim 14).

The Gingeras *et al.* reference discloses a chip-based species identification using array and bar code and an apparatus comprising a computer system and bar code reader (Figure 14, 15 and 32 and column 7). Gingeras does not disclose an apparatus detecting a metallic precipitate formed at the location of the bound target as recited in Claim 14.

In addition, as discussed above and in the accompanying Declaration and Exhibits, the detection method of the present invention has significant advantages over the methods taught in the cited references.

Accordingly, the cited references do not render the claimed invention obvious.

V. Conclusion

Claim 2 has been canceled without prejudice, Claims 1 and 14 have been amended, and new Claim 33 has been added. Support for new Claim 33 is found in the specification as filed on page 4, line 5, page 6, lines 23 to 26 and within the Examples. Support for the amendment to Claim 1 is found in the specification as filed on page 5, line 30 to page 6, line 3, page 8, line 22 to page 10, line 23 and within the Examples. Support for the amendment to Claim 14 is found in the specification as filed on page 10, lines 24-30.

In view of the foregoing amendments, remarks, and accompanying Declaration, Applicant respectfully asserts that the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

The changes made to the specification, the Abstract and the claims by the current amendment, including insertions and **[deletions]**, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment. No new matter has been added herewith.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Feb. 27, 2002

By: Daniel Hart

Daniel Hart
Registration No. 40,637
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(619) 235-8550

O:\DOCS\MCM\MCM-1647.DOC
112601

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Abstract:

The abstract on page 29, beginning at line 1, has been amended as follows:

ABSTRACT

METHOD FOR THE IDENTIFICATION AND/OR THE QUANTIFICATION OF A TARGET COMPOUND OBTAINED FROM A BIOLOGICAL SAMPLE UPON CHIPS

The present invention is related to a method for the identification and/or the quantification of a target compound obtained from a sample, preferably a biological sample, comprising the steps of**[**:

-]putting into contact the target compound with a capture molecule in order to allow a specific binding between **[said]**the target compound with a capture molecule, **[said]**the capture molecule being fixed upon a surface of a solid support according to an array comprising a density of at least 20 discrete regions per cm^2, each of **[said]**the discrete regions being fixed with one species of capture molecules, **[**

-]performing a reaction leading to a precipitate formed at the location of **[said]**the binding, determining the possible presence of precipitate(s) in discrete region(s), and **[**

-]correlating the presence of the precipitate(s) at the discrete region(s) with the identification and/or a quantification of **[said]**the target compound.

In the Claims:

1. **(Amended Three Times)** A method for the identification and/or the quantification of a target compound obtained from a sample, comprising the steps of:

putting into contact the target compound with a capture molecule in order to allow a specific binding between said target compound with a capture molecule, said capture molecule being fixed upon a surface of a solid support according to an array comprising a density of at least 20 discrete regions per cm^2, each of said discrete regions being fixed with one species of capture molecules**[**,**]**;

performing a reaction leading to formation of a precipitate formed at the location of said binding by the deposit of a metallic **[within a few micrometers from the bound target]** compound**[,]**;

determining the possible presence of precipitate(s) in**[said]** discrete region(s)**[,]**; and correlating the presence of the precipitate(s) at **[said]**the discrete region(s) with the identification and/or a quantification of said target compound.

14. **(Amended Three Times)** A diagnostic and/or quantification apparatus comprising:

a solid support comprising an array comprising at least 20 discrete regions per cm^2, each of said regions being fixed with one species of a capture molecule which recognizes a target compound, target compounds bound to some of said capture molecules, and a precipitate present **[within a few micrometers]**at the location of said bound target compounds;

a detection and/or quantification device for detecting said precipitate; and

a computer programmed to collect the results obtained from said detection and/or quantification device.